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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 52

Application Number: 08/402,394
Filing Date: March 10, 1995
Appellant(s): DORSCHUG et al.

Carol P. Einaudi
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 19 October 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 21-23, 25-27, 31 and 33-42 do stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4,916,212	MARKUSSEN	4-1990
4,801,684	GRAU	1-1989
4,639,332	GRAU	1-1987
5,087,564	MAI	2-1992
EPO 163,529	MARKUSSEN	12-1985

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 21 and 33-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332).

Markussen et al. ('212) discloses insulin precursors of the form B(1-29)-X_n-Y-A(1-21). "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). This precursor protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin. (See '212 at column 2, line 65, through column 3, line 46; Examples 11, 13, and 16; and claims.) Fusion proteins and their cleavage from the precursor are disclosed. (See column 5, lines 11-20.) DNA sequence encoding the insulin precursor, expression vectors, transformed cells, and recombinant methods of production in yeast (as well as E. coli holding plasmids

encoding the desired insulin precursors) are also disclosed and claimed. Markussen et al. ('529) teaches essentially the same invention. (See pages 5-6, 8; Table 1; Example 11, page 26; Example 13, page 29; Example 16, page 30; claims.) The Markussen references do not specifically teach the preparation of mono-Arg-insulin which includes the use of trypsin as cleavage agent for generation of mono-Arg-insulin.

The miniproinsulin of the instant application is directed to a single peptide chain of the formula B(1-30)-Arg-A(1-21). The amino acid at position 30 in native human insulin is Thr. This position is equivalent to the "X" of Markussen et al.

Goeddel et al. teach producing recombinant fusion proteins of insulin precursors to another protein and cleaving them. The reference further teaches making a fusion protein with an insulin variant in which the C chain of insulin contains only six amino acids. (See page 6, line 19 through page 8, line 2; abstract; claims; pages 26-27.) Goeddel et al. also teaches production in E. coli. With regard to fusion proteins, it is noted that E. coli has long been used to produce desirable precursors to insulin and that fusion proteins are often used for small peptides.

Grau ('684) teaches using trypsin and carboxypeptidase B simultaneously to produce mature insulin from proinsulin. (See column 5, lines 49-59.)

Grau ('332) teaches that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31. This insulin-Arg^{B31}-OH derivative is stable to further tryptic degradation. Enzymes having both tryptic and carboxypeptidase B activity are required to

produce insulin. (See column 1, lines 1-32; column 2, lines 10-12.) The intermediate disclosed by Grau ('332) is the mono-Arg-insulin of formula II in the instant claims.

Markussen et al. suggest the claimed miniproinsulin precursor, DNA sequences encoding it, vectors, host cells and process for preparation where "X" is Thr, "n" is 1, and "Y" is Arg. This is a very similar structure to the preferred embodiment B(1-29)-Ser-Lys-A(1-21). The claimed generic formula of the prior art encompasses Applicant's claimed composition in method step (a). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use this particular embodiment as suggested by Markussen et al. for the production of mono-Arg-insulin as taught by Grau ('332 and '684) because mono-Arg-insulin is exceptionally stable to further tryptic degradation (column 2, lines 10-12 of Grau '332) and makes this species of miniproinsulin an ideal and obvious choice for use in the preparation of mono-Arg-insulin. Furthermore, it would have been obvious to make fusion proteins as taught by Goeddel et al. using the insulin precursor, DNA sequences, and vectors taught by either Markussen et al. reference for the production of the mono-Arg-insulin of Grau and to cleave the fusion protein to release the desired protein as taught by Goeddel et al. One would have been motivated by the known benefits of producing small peptides as fusion proteins in bacterial and yeast hosts and the success with another insulin variant in which the C chain is shortened and because the usefulness of fusion proteins is suggested by Markussen et al. It would have been obvious to prepare mono-Arg-insulin by expressing a DNA molecule encoding miniproinsulin in bacteria as taught and suggested by

Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce mono-Arg-insulin. One would have been motivated to produce this stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes. Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

2. Claims 25 and 37-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) as applied to claim 21 above, further in view of Mai et al.

The disclosures of Markussen et al., Goeddel et al. and Grau are as described above. These references do not specifically teach the bridging member Met-Ile-Glu-Gly-Arg of step (a) in claim 25.

Mai et al. teach that it would have been well known in the art to use common cleavage sites in fusion proteins. The reference teaches that cyanogen bromide cleaves after the amino acid Met and that factor Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. (See column 3, line 14, through column 4, line 35, especially column 3, line 67, through column 4, line 1; and column 9, lines 7-19.)

It would have been obvious to make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg as taught in Mai et al. for the production of mono-Arg-insulin of Grau. Markussen et al. suggest making fusion proteins that can be cleaved as does Goeddel et al. The recited sequence of the claim includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins and would have been well known to the skilled artisan. One would have been motivated to make a fusion protein for the reasons taught by Markussen et al., Goeddel et al., and Mai et al. and to use this construct in the method of making mono-Arg-insulin of Grau for the advantages taught therein, absent evidence to the contrary. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made.

3. Claims 22-23 and 40-41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332). Appellant states that this rejection was not previously made over claims 40-41, and would appear to be an oversight. However, the claims were not previously included in this ground of rejection because of the outstanding 112 rejection. In light of the amendment to the claims, the 112 rejection has been overcome, but the 103 rejection is now applicable and the claims are included in this ground of rejection. This is not a new ground of rejection because the rejection was of record in the final Office action.

The disclosures of Markussen et al., Goeddel et al. and Grau are as described above. Markussen et al. do not teach a method of making insulin using both trypsin and carboxypeptidase B to convert miniproinsulin to mono-Arg-insulin and then to insulin.

It would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. (having the formula B(1-30)-Arg-A(1-21)) first to mono-Arg-insulin and then to insulin. Grau ('332) teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in order to produce insulin from the precursor of Markussen et al. for treating diabetes. One would also have a reasonable expectation of success in obtaining insulin from the miniproinsulin precursor of Markussen et al. because the miniproinsulin having the formula B(1-30)-Arg-A(1-21) is very similar to the preferred embodiment of Markussen et al. and because this miniproinsulin would provide for the stable mono-Arg-insulin of Grau in the process of making insulin. It also would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Finally, claim 23 requires that the trypsin and carboxypeptidase B be added in the same vessel; Grau '684 teaches the process wherein trypsin and carboxypeptidase B were added together

(i.e. in the same vessel) and resulted in the production of mature insulin from proinsulin (see column 5, lines 57-59). Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

4. Claims 26-27 and 31 are rejected (and newly added claim 32 is rejected) under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) as applied to claims 22-23 above.

The disclosures of Markussen et al., Goeddel et al., Grau and Mai et al. are as described above. None of these references teach the method of the claims in its entirety. Claims 26-27 and 31 are directed to methods using both trypsin and carboxypeptidase B to convert miniproinsulin to mono-Arg-insulin and then to insulin, including a bridging member Met-Ile-Glu-Gly-Arg between the fusion protein and the miniproinsulin. Claim 31 also includes the limitation of "without formation of substantial amounts of insulin Des-B30.

It would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. (having the formula B(1-30)-Arg-A(1-21)) first to mono-Arg-insulin and then to insulin. Grau ('332) teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. One would have been motivated to use both trypsin and carboxypeptidase B in

order to produce insulin from the precursor of Markussen et al. for treating diabetes. One would also have a reasonable expectation of success in obtaining insulin from the miniproinsulin precursor of Markussen et al. because the miniproinsulin having the formula B(1-30)-Arg-A(1-21) is very similar to the preferred embodiment of Markussen et al. and because this miniproinsulin would provide for the stable mono-Arg-insulin of Grau in the process of making insulin. It also would have been obvious to make the miniproinsulin of Markussen et al. as a fusion protein using the cleavable sequence Met-Ile-Glu-Gly-Arg as taught in Mai et al. for the production of mono-Arg-insulin of Grau. Markussen et al. suggest making fusion proteins that can be cleaved as does Goeddel et al. The recited sequence of the claim includes cleavage sites for cyanogen bromide and factor Xa that would have been commonly used in fusion proteins and would have been well known to the skilled artisan. One would have been motivated to make a fusion protein for the reasons taught by Markussen et al., Goeddel et al., and Mai et al. and to use this construct in the method of making mono-Arg-insulin of Grau for the advantages taught therein, absent evidence to the contrary. It also would have been obvious to one of ordinary skill in the art at the time the invention was made to precipitate the resulting mono-Arg-insulin for the isolation of the desired product as taught by Markussen '212 (column 18, lines 42-68). Claim 27 requires that the trypsin and carboxypeptidase B be added in the same vessel; Grau '684 teaches the process wherein trypsin and carboxypeptidase B were added together (i.e. in the same vessel) and resulted in the production of mature insulin from proinsulin (see column 5, lines 57-59). Lastly, claim 31

recites "without formation of substantial amounts of insulin Des-B30". One of ordinary skill in the art would not expect the method of Grau for the production of insulin from miniproinsulin and mono-Arg-insulin to result in the formation of substantial amounts of Des-B30 insulin, nor are there any steps in the instant claims which would distinguish from the prior art in resulting in different amounts of Des-B30 insulin, absent evidence to the contrary. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made.

5. Claims 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. ('828) either in view of Grau ('684) and Grau ('332).

The references are as described above. The intermediate disclosed by Grau ('332) is the mono-Arg insulin of formula II. It would have been prima facie obvious to one of ordinary skill in the art to prepare the mono-Arg-insulin by expressing a DNA molecule encoding miniproinsulin in either bacteria or yeast as taught by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce mono-Arg-insulin. One would have been motivated to produce a stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes. One would further be motivated to make the mono-Arg-insulin because Grau ('332) teaches that mono-Arg-insulin is resistant to further tryptic degradation, and would therefore, be a stable intermediate for the future formation of insulin.

(11) Response to Argument

(1) Appellant argues at page 13 of the Brief that Markussen discloses a generic formula which encompasses millions of compounds and that there is no suggestion to select the particular species of miniproinsulin, wherein X=Thr and Y=Arg. This argument is not persuasive for more than the fact that these amino acids are conservative substitutions for Markussen's preferred embodiment of X=Ser and Y=Lys. As stated above, the general formula of Markussen is B(1-29)-$(X_nY)_m$-A(1-21) and the preferred embodiment of Markussen is B(1-29)-Ser-Lys-A(1-21). The amino acid at position 30 in native human insulin is Thr, which is equivalent to the "X" of Markussen et al. The only 2 amino acids suggested by Markussen for "Y" are lysine and arginine. The particular embodiment of B(1-29)-Thr-Arg-A(1-21) is encompassed by Markussen and is very similar to the preferred embodiment of B(1-29)-Ser-Lys-A(1-21). The cleavage of this insulin precursor, as taught by Grau, results in the production of mono-Arg-insulin which is exceptionally stable to further tryptic degradation (column 2, lines 10-12 of Grau '332) and makes this species of miniproinsulin an ideal and obvious choice for use in the preparation of mono-Arg-insulin. Although the formula of Markussen encompasses many emobodiments, the teachings of Grau would lead one of ordinary skill in the art to this particular embodiment and motivate one to make this particular embodiment. One would have a reasonable expectation that it would fold in a manner that would permit the proper disulfide bonding of the insulin chains because the preferred embodiment of Markussen is of a similar structure (i.e. conservative amino acid substitutions),

and therefore, one would expect it to function in a similar manner in the formation of mature insulin.

Appellant argues at page 14 that the examples of Markussen do not include embodiments which end with Arg and that if Thr were selected for the "X" position, that there would need to be several more amino acids in the C chain. This argument is not persuasive because, although Markussen's examples do not include Arg, the amino acid selection for the "Y" position only include two choices; Lys or Arg. As stated previously, one would be motivated to select Arg because this would provide for mono-Arg-insulin which is a desireable product as taught by Grau. Additionally, the selection of Thr for "X" provides for an insulin precursor which has the native B chain of human insulin because the "X" position is equivalent to the B-30 position of insulin. The structural similarity of the B(1-29)-Thr-Arg-A(1-21) to the preferred embodiment B(1-29)-Ser-Lys-A(1-21) of Markussen suggests that additional amino acids in the C-chain are not needed, as asserted by Appellant, for the reasons provided above.

Appellant argues that "unless one knew the exact composition disclosed in the instant specification in advance, there would be no incentive to achieve this claimed composition". In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed

invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). However, motivation to arrive at the particular embodiment of B(1-29)-Thr-Arg-A(1-21) comes from Grau's teaching of the stability of mono-Arg-insulin and the desireability of human insulin.

Appellant argues at page 15 of the Brief that Markussen teaches away from Appellant's claimed mini-proinsulin construct based on the methods of Markussen which convert the precursors to a B(1-29) form and add the Thr via a transpeptidation reaction. However, Markussen was not cited for its method of making insulin, but only for its methods of making the precursor insulin compound of the formula B(1-29)-$(X_nY)_m$-A(1-21). Appellant's arguments spanning pages 15-18 are directed to the fact that Markussen intended the X position of the formula to be part of the C-peptide which would be excised in their methods, and therefore "the skilled artisan would have had no reasonable expectation of success in achieving Appellants' claimed B(1-30)-Arg-A(1-21) compound". This argument is not persuasive because Markussen was not relied upon for the method of obtaining insulin or mono-Arg-insulin. Markussen was relied upon for the teaching of a single precursor peptide chain, fusion proteins and their cleavage from the precursor, DNA encoding the insulin precursor, expression vectors, transformed cells, and recombinant methods of production in yeast. The teachings and methods of Grau were relied upon for the production of mono-Arg-insulin and insulin from the precursor protein, wherein the specific embodiment which is

encompassed by Markussen is made obvious by the teachings of the stability of mono-Arg-insulin by Grau.

Appellant continues to argue the method of Markussen (see pages 18-19). Appellant argues that the disclosure of Grau regarding the stability of mono-Arg-insulin is not motivation to convert the mini-proinsulin of Markussen to a mono-Arg-insulin. This argument is not persuasive because it relies on the method of Markussen which utilizes a transpeptidation step. From the teachings of Grau, one can use the mini-proinsulin of Markussen in the method of Grau to obtain a very stable intermediate, mono-Arg-insulin, which can then be converted to insulin. The fact that the intermediate is very stable is clear motivation to make it as taught by Grau, and the fact that the method does not require the additional transpeptidation step of Markussen is further motivation for using the method of Grau.

Appellant again argues (bottom of page 20) inproper hindsight, however,it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Markussen was not cited for the method of making insulin, but for the production of insulin precursors. It is appreciated that Markussen received a patent on a method of making insulin using a B chain of B(1-29) and a transpeptidation step, but Markussen was not cited for this teaching.

Appellant asserts that the prior art art would not have suggested mono-Arg-insulin for the production of human insulin because Thim et al. teaches that trypsin would not cleave an Arg-Arg or Lys-Arg bridge between the B and A chains. This argument is not persuasive because Applicants' invention does not required cleavage of B and A chains linked by Arg-Arg or Lys-Arg by trypsin alone, therefore the negative teaching of Thim et al. as to the necessity of another protease in addition to trypsin would not be applicable to the instant invention. The Arg linking the B and A chains is bound to Thr and Gly, respectively in the instant invention and therefore, this argument does not appear to have a basis in fact. Additionally, Grau '332 specifically teaches using trypsin for this purpose and would contradict the negative teachings of Thim et al.

Appellant argues that because the method of Markussen does not utilize trypsin for generation of insulin, then the invention must not be obvious. However, if Markussen had used trypsin, the invention may have been anticipated. The issue is whether the invention as claimed is obvious at the time is was made over the prior art references which are cited in the rejection, not why one reference teaches one method of producing insulin when there was an alternative method available.

Appellant argues at page 22 that the skilled artisan would not expect trypsin to cleave at a single Arg residue. This argument is not persuasive because Grau teaches this cleavage. Appellant further argues that there is no reasonable expectation that the simultaneous addition of trypsin and carboxypeptidase would work with mini-proinsulin because Grau('684) used

procine proinsulin and not the compound of the instant invention. This argument is not persuasive because the claims which are rejected do not require the addition of carboxypeptidase B, which would provide insulin and not mono-Arg-insulin of the claims. Grau ('332) specifically teaches the addition of trypsin to arrive at mono-Arg-insulin, therefore, the arguments regarding the enzyme cut rate are not persuasive.

(2) Appellant argues that the claims include "a novel and nonobvious bridging member in the fusion protein". This argument is not persuasive because the bridging member is the combination of Met and the peptide Ile-Glu-Gly-Arg. It was known in the prior art that cyanogen bromide cleaves after Met and that factor Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. Therefore, the construct of Met-Ile-Glu-Gly-Arg merely combines known cleavage sites in the prior art and one of ordinary skill in the art would have been aware of these cleavage sites and therefore, the construct would have been prima facie obvious to one in the fusion protein art, absent evidence to the contrary. Appellant argues that Mai does not suggest using this sequence in a fusion peptide. This is not persuasive because Mai does teach the general concept of using site-specific release of peptides from fusion proteins using enzymes and peptidases, with the teaching of factor Xa and its cleavage site. The suggestion to add this peptide to a fusion protein comes from the general teaching of Mai to make heterologus proteins by utilizing a fusion protein comprising a heterologous peptide linked to an endogenous protein at a junction site, wherein use of an enzyme or peptidase is used to liberate the heterologous peptide from the fusion protein (see column 7, lines 1-14). The fact that Mai

exemplifies recA and a enzyme substrate does not teach away from using any known enzyme and enzyme substrate, including factor Xa and Ile-Glu-Gly-Arg.

Appellant again argues at page 25 the combination of trypsin and carboxypeptidase, which are not limitations of the claims being rejected under these references.

(3) Appellant again argues the prosecution history of Markussen as a basis for lack of motivation to make the claimed invention. However, as stated previously, this argument is based on the method of Markussen, which is not relied upon for the rejection. Appellant agues that the teachings of Grau is not sufficient for modifying the Markussen method. Again, it is not the Markussen method which is relied upon for the rejection, but rather the generic mini-proinsulin formula.

(4) Appellant's arguments regarding Markussen and Grau have been presented earlier and answered. Appellant again argues that the bridging member is "novel and unobvious". This argument has also already been presented and answered (see #2 above).

(5) Appellant's arguments regarding Markussen and Grau have been presented earlier and answered.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

C.S.
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